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TITLE: Failure of Cetirizine and Fexofenadine to Prevent Motion Sickness

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ABSTRACT: To determine the effectiveness of two "second generation" antihistamines in modulating motion sickness induced by Coriolis vestibular cross coupling stimulation

Il y a un résumé français ici.

IDENTIFIERS: second generation antihistamines;nausea;motion sickness

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Important Notices

Ambulatory Care

Failure of Cetirizine and Fexofenadine to Prevent Motion Sickness

Bob S Cheung, Raquel Heskin, and Kevin D Hofer

OBJECTIVE: To determine the effectiveness of 2 second-generation antihistamines in modulating motion sickness induced by Coriolis vestibular cross-coupling stimulation.

METHODS: This prospective, randomized, double-blind, crossover, placebo-controlled study was conducted in 18 healthy adults. Subjects were exposed to Coriolis vestibular cross-coupling in the laboratory using the Staircase Profile Test for baseline susceptibility and when under the influence of cetizirine, fexofenadine, and placebo. Subjective evaluation of sickness symptoms was based on the Graybiel diagnostic criteria of acute motion sickness, Golding's scale, and the Coriolis Sickness Susceptibility Index.

RESULTS: Repeated measures ANOVA and Friedman nonparametric ANOVA of rank tests revealed that there were significant differences in symptom assessments based on Graybiel's diagnostic criteria ($p \leq 0.001$), subjective symptoms of motion sickness ($p \leq 0.001$), and state-anxiety ($p \leq 0.001$) before and after motion exposure. However, there are no significant differences between the baseline susceptibility to motion sickness and treatment with placebo, cetirizine, or fexofenadine.

CONCLUSIONS: The failure of the second-generation antihistamines cetirizine and fexofenadine to prevent motion sickness suggests that the therapeutic actions of this class of antihistamines against motion sickness may be mediated through central versus peripheral receptors. The sedative effect of other antihistamines, such as hydroxyzine, may play a more significant role in alleviating motion sickness than previously thought.

KEY WORDS: emesis, motion sickness, nausea, second-generation antihistamines.

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The 2 most commonly used classes of antimotion sickness drugs are the antihistamines and anticholinergics. Numerous antihistamines (e.g., cinnarizine, cyclizine, dimenhydrinate, diphenhydramine, meclizine, promethazine) have been in clinical use as antiemetic/antivertigo drugs since 1941.[1] These agents bind to both peripheral and central histamine$_1$ (H_1) receptors, as well as anticholinergic receptors, and produce an antiemetic/antimotion sickness effect that is presumably the result of central inhibition of these pathways. Considerable variation exists among individuals in their response to antihistamines, but the most common adverse effect is drowsiness due to central nervous system (CNS) depressant properties of these agents. Drowsiness may inadvertently affect performance and pose unwanted hazards during activities in which these agents may be used (e.g., driving, sailing, flying). In addition, these agents have limited durations of action and some of them (i.e., diphenhydramine, promethazine) also exhibit cross reactivity with cholinergic responses, resulting in a relatively higher incidence of anticholinergic adverse effects. Therefore, there is merit to the experimental

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testing of second-generation antihistamines, which bind selectively to peripheral H_1 receptors and are less likely to cause drowsiness, as well as having a relatively longer duration of action compared with traditional antimotion sickness compounds.

Although terfenadine is no longer available on the US market due to an increased risk of ventricular arrhythmias,[2] 1 study showed that a single large dose of terfenadine 300 mg had a statistically significant ($p < 0.05$) therapeutic effect on motion sickness.[3] Cetirizine, a piperazine derivative and active carboxylic acid metabolite of hydroxyzine, is another peripherally selective H_1 receptor blocker that has reduced access to the CNS but also produces central activity over the therapeutic range.[4] The onset of therapeutic activity is <1 hour and the duration of action is 24 hours. Several studies have shown that cetirizine is primarily responsible for the antihistaminic actions of hydroxyzine, whereas the sedating effects correlate best with the parent compound.[5] In a double-blind study, hydroxyzine 25 mg twice daily was shown to be effective in controlling nausea and vomiting during early pregnancy[6] and for controlling motion sickness[7]; the only adverse effect reported was mild drowsiness. A survey by Einarson et al.[8] reported that 60 pregnant women who took cetirizine 10 mg/d to control allergies in the first trimester of pregnancy appeared to have a lower rate of nausea and vomiting than the control group. The etiology of nausea and vomiting during pregnancy has not yet been clarified. However, treatment of hyperemesis gravidarum by electrical stimulation of the vestibular system was found to be helpful in reducing symptoms,[9] which strongly suggests the clinical similarity of morning sickness and motion sickness.

In light of these findings, the purpose of the present study was to investigate the efficacy of cetirizine and fexofenadine hydrochloride, both commercially available second-generation antihistamines, in the prevention of motion sickness in a group of healthy men and women using 3 different test methods for evaluating subjective assessments of symptoms and severity of motion sickness. Fexofenadine was chosen as the comparative agent because it is the metabolite of terfenadine, is devoid of activity on the myocardial potassium channel, and is negligibly metabolized.[10]

Methods

SUBJECTS

Eighteen healthy subjects (13 men, 5 women) between the ages of 21 and 48 years participated in this study. They had no known history of ophthalmologic, oculomotor, or vestibular disorders, and they had neither spontaneous nystagmus nor Romberg's sign with eyes opened or closed. Approval for the study was obtained from the Defence Research and Development Canada (DRDC)-Toronto Human Ethics Committee. All subjects gave informed consent after obtaining medical approval to participate from a DRDC-Toronto physician. Since the experiment could be potentially harmful to a fetus, all women consented to administration of a serum pregnancy test as part of the medical procedure prior to commencement of this experiment. Instructions were given to all subjects to strictly abstain from alcohol, tobacco, and over-the-counter or prescribed medication for at least 24 hours prior to the study.

STUDY DESIGN

A randomized, placebo-controlled, double-blind crossover design was employed to assess the efficacy of single doses of cetirizine 10 mg, fexofenadine 60 mg, and placebo (10 mg of cornstarch) in 18 subjects as an antimotion sickness drug. The participants were arbitrarily assigned a subject number from 1 to 18, and the 3 treatments were administered to the subjects according to a counterbalanced sequence using a pseudo Latin-square. Respective compounds were of identical appearance and each compound was given orally 1 hour before motion exposure. The test procedure used included a predrug evaluation of baseline susceptibility to the specific stimulus of Coriolis vestibular cross-coupling. The Coriolis vestibular cross-coupling test was performed using the motion sickness platform at DRDC-Toronto rotating about the spinal axis of the subject at a prescribed velocity. A blindfolded subject restrained by a 4-point harness was asked to make head-movements in and out of the plane of body rotation at a specific time interval. If the subject makes head movements during such rotations, this maneuver produces unusual stimulation of the semicircular canals.

The combined effect of cupula deflection of the semicircular canals is that of a suddenly imposed angular rotation in a plane in which no angular acceleration relative to the subject has occurred; this results in sensations of disorientation, and motion sickness may occur.[11] Coriolis cross-coupling stimulation is a validated, reproducible procedure that is routinely used in our laboratory and others[3] to study motion sickness.

PROTOCOL

Coriolis cross-coupling was induced using a Staircase Profile to determine baseline motion sickness susceptibility and to evaluate the effectiveness of cetirizine, fexofenadine, and placebo in preventing motion sickness. The Staircase Profile is a standardized motion sickness test procedure in which the rotational velocity of the chair is progressively increased. Beginning at a chair velocity of 5 rpm (or 30°/s), the subjects executed standardized head movements in each of the 4 cardinal directions with their eyes closed. These head movements were performed in sets, with each set consisting of 5 head movements (front, right, back, left, front). Each set is separated by a 20-second period of no head movement. The chair velocity was increased in 5-rpm steps with 40 head movements (or 8 sets of head movements) performed at each step until the subject reached definite nausea and wanted to stop (level 7 on the Golding's scale) or a terminal velocity of 30 rpm (180°/s) is reached.

This procedure was employed at baseline and again ≥7 days later within 1 hour of drug and placebo administration. Each subject was exposed to 4 tests over 4 weeks (baseline susceptibility and 3 randomized drug treatments). An interval of at least 7 days between tests was employed to avoid habituation to the stimulus.

This Staircase profile has been performed previously in our laboratory and by other investigators,[12,13] where Coriolis stress (CS) is directly proportional to the number of head movements (HMs) made. The Coriolis Sickness Susceptibility Index (CSSI) can be calculated by multiplying the number of head movements made at each rotational velocity by the CS value determined at the rotational velocity by $\log CS = 2.09065 (\log w)^{-3.08572}$ (where w is the angular velocity rotation/min) and then summing the individual products. This process can be simplified and approximated by deriving the integral of CS with respect to HM. The integral of this function is shown to closely approximate the cumulative stress endured by making 40 HMs at each rpm and is based on empirical observations of Miller and Graybiel[14]:

$$CSSI = \int_0^{HM} CSd(HM) = 2.42230 \times 10^{-7} \times (HM)^{3.09065}$$

The efficacy of the compounds in modulating motion sickness was determined by the CSSI across all treatment groups and relative to baseline susceptibility tests. In addition, the efficacy of the compounds was also determined by subjective symptom assessments. Immediately before and after motion exposure, Graybiel's diagnostic criteria[15] for grading severity of sickness and a modified rating scale based on these criteria was employed to quantify subjective symptoms and severity of sickness. The same rater administered these assessments throughout the study. Great reliance has been placed on the 5 cardinal symptoms (nausea, pallor, cold sweating, increased salivation, drowsiness) of motion sickness, and not more than 1 score for any symptom was used in any evaluation.

During motion exposure, the subjective scale used by Golding and Kerguelen[16] was employed to solicit the subjective symptoms of motion sickness from the subject. Specifically, each subject rated their degree of motion sickness after each HM on the following scale: 1 = no symptoms, 2 = any symptoms (slight), 3 = mild symptoms (e.g., stomach awareness but no nausea), 4 = mild nausea, 5 = mild to moderate nausea, 6 = moderate nausea but can continue, 7 = moderate nausea and wants to stop. Subjects memorized this scale before commencement of the trial. They were informed that, although the scale was ordinal, they did not have to follow the scale in the written sequence, but rather to pair symptoms they experienced at a particular instant with a specific level on the scale. The S anxiety scale[17] was used to assess the level of state-anxiety as an indicator of change in transitory anxiety experienced by the subjects. It was also administered before and after each trial.

STATISTICAL ANALYSIS

Data were analyzed by repeated measures ANOVA using Statistica by Statsoft, with the significance level α set as ≤ 0.01. All post hoc testing was completed using planned comparisons. The p values for factors with >2 levels were adjusted using Greenhouse–Geisser's Σ correction factor. For subjective symptoms assessment, a 4 (baseline susceptibility test, 3 treatment groups) × 2 (before and after motion exposure) repeated measures ANOVA was performed on the subjective evaluations of severity of motion sickness (based on Graybiel's diagnostic criteria) and subjective symptoms of motion sickness (modified Graybiel criteria). Friedman nonparametric ANOVA of ranks and Wilcoxon signed-ranked tests were also used to assess the symptoms and severity of motion sickness before and after motion exposures. A 1-way (treatment) repeated measures ANOVA was performed on the CSSI.

Results

The main effects before and after motion exposure were significant based on Graybiel's diagnostic criteria [$F(1, 17) = 94.63$; $p \leq 0.001$], subjective symptoms of motion sickness [$F(1, 17) = 52.56$; $p \leq 0.001$], and state-anxiety [$F(1, 17) = 23.73$; $p \leq 0.001$]; however, the main effects of treatment groups and the interactions between the treatment groups before and after motion exposure were not significant (Figures 1, 2, 3).

The results of the Friedman nonparametric ANOVA of ranks were similar to those of the parametric analyses. Significant differences were observed among factors in each of the subjective symptoms assessment: based on Graybiel's diagnostic criteria [$\chi^2(18, 7) = 96.79$; $p < 0.001$], subjective symptoms of motion sickness [$\chi^2(18, 7) = 89.13$; $p < 0.001$], and anxiety [$\chi^2(18, 7) = 47.33$; $p < 0.001$]. Using Wilcoxon signed-ranked tests, significant contrasts were found between before and after motion exposure evaluations in each test condition for each subjective symptom assessment measure ($p < 0.001$). However, no significant differences were observed across the treatment groups.

No significant differences were found among baseline susceptibility, cetirizine, fexofenadine, and placebo conditions (Figure 4). The above results reveal that subjects displayed more outward signs of motion sickness, reported more subjective symptoms of motion sickness, and were more anxious following the Coriolis vestibular cross-coupling stimulation as compared with before motion exposure. However, subjective assessments of motion sickness and the CSSI were not affected by any of the treatments used in this study.

Discussion

The vomiting center located in the parvicellular reticular formation of the brain stem[18] receives input from numerous sources to activate the vomiting reflex. Neurophysiologic evidence suggests that H_1 receptors were detected in high densities in the nucleus tractus solitarius and in the dorsal motor nucleus of the vagus and in moderate densities in the nucleus ambiguus,[19,20] which constitutes the major afferent pathways involved in vomiting. These findings are consistent with the use of antihistamines as 1 of the common remedies for motion sickness. Chemically, antihistamines are of a diverse nature: several first-generation H_1-receptor antagonists with structures based on piperazine (cyclizine, cinnarizine) or ethanolamine (dimenhydrinate, the chlorotheophylline salt of diphenhydramine) have demonstrated sufficient therapeutic usefulness in treating

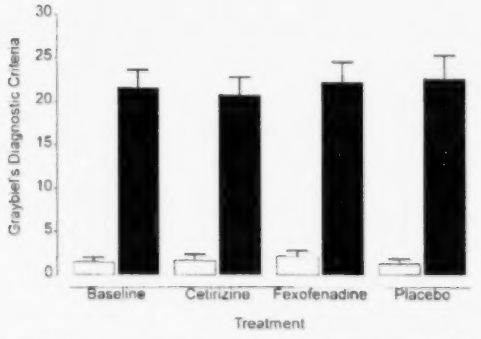

Figure 1. Mean scores of symptoms and severity of motion sickness before and after Coriolis vestibular cross-coupling stimulation based on Graybiel's diagnostic criteria for acute motion sickness. There was a significant increase in symptoms of motion sickness after motion exposure ($n = 18$; $p < 0.001$); however, there was no significant difference between the 4 conditions. □ = pre, ■ = post. Error bars are SEM.

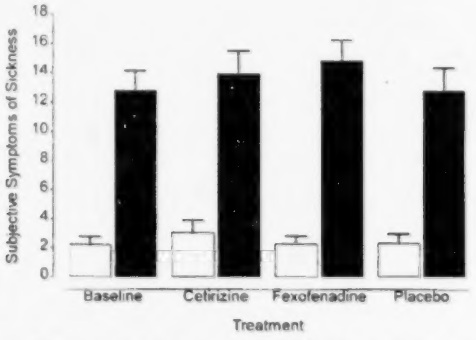

Figure 2. Mean scores of subjective symptoms of motion sickness before and after Coriolis vestibular cross-coupling stimulation. Similar to results depicted in Figure 1, there was a significant increase in the symptoms of motion sickness after motion exposure ($n = 18$; $p < 0.001$), but no significant difference between the 4 conditions. □ = pre, ■ = post. Error bars are SEM.

nausea and vomiting from motion sickness and other vestibular disturbances, as well as morning sickness and postoperative vomiting. For example, promethazine has been found to be effective treatment for antimotion sickness as early as 1941.[1] Using the Coriolis cross-coupling technique, Wood and Graybiel[21] also demonstrated the effectiveness of promethazine in preventing motion sickness. Although the major adverse effects of using centrally acting antihistamines are sedation and decreased motor functions, the relationship between the sedative action and the antiemetic effectiveness in these compounds is not clear.

The etiology of nausea and vomiting during early pregnancy has yet to be clarified, although allergic, endocrine, intestinal, metabolic, and psychosomatic factors have been implicated. On the other hand, the etiology of motion sickness suggests that the pathophysiology is rooted in an organic, dynamic, and heterogeneous process.[22] This process is exemplified by a neurosensory mismatch between the different systems (visual, vestibular, somatosensory) responsible for spatial orientation. Sedation, such as that seen with hydroxyzine, may significantly limit sensory stimulation and also prevent sensory input from reaching the integrator of the spatial orientation systems. As described in the *Introduction*, cetirizine may be primarily responsible for the antihistamine action of hydroxyzine.[5] In view of our findings that cetirizine is ineffective in modulating motion sickness, it is possible that the sedative effect of hydroxyzine and, possibly, other centrally acting histamines contributes significantly to their antimotion sickness property.

A very high (300 mg) single dose of terfenadine was shown to have therapeutic effect in the control of nausea,[3] which suggests that other peripherally acting compounds might also possess antimotion sickness efficacy. However, in our study, a usual oral dose (60 mg) of fexofenadine failed to control symptoms of motion sickness. Another nonsedating H_1 antagonist, astemizole, was also found to be ineffective in alleviating motion sickness,[23] although it gains access to the vestibular apparatus and the chemoreceptive trigger zone.[24] Finally, although both morning sickness and motion sickness affect the vomiting center of the brain, the afferent pathways involved in the vomiting reflex of morning sickness and motion sickness could be different. Therefore, pharmacologic intervention to these syndromes may vary.

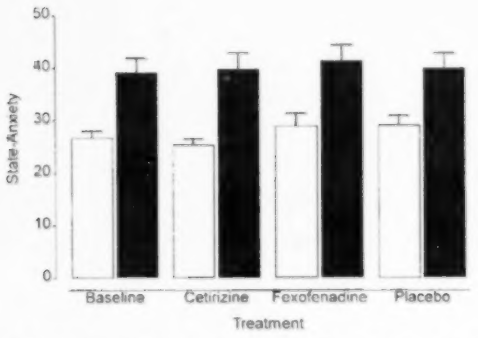

Figure 3. Mean score of state-anxiety before and after motion exposure, showing significant increase after motion exposure ($n = 18$, $p < 0.001$), but no significant difference between the 4 conditions. □ = pre, ■ = post. Error bars are SEM.

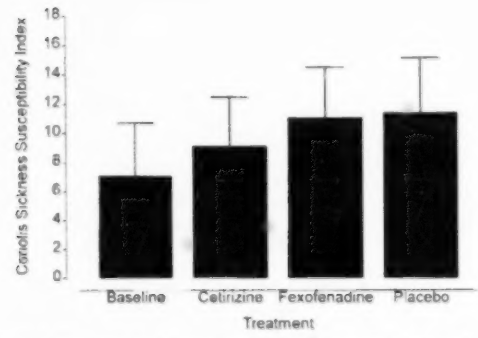

Figure 4. Mean Conolis Sickness Susceptibility Index across the 4 conditions. Baseline susceptibility was administered to all the subjects prior to drug testing. This might have contributed to the lower score seen in the figure as naive subjects tend to limit their exposure to the cross-coupling stimulus in their initial exposure. The drug conditions and the placebo trial were randomized. Nevertheless, there were no significant differences across all 4 conditions. Error bars are SEM.

Summary

Our study suggests that cetirizine 10 mg/d and fexofenadine 60 mg/d did not significantly influence the amount of vestibular cross-coupling stress that subjects could tolerate before reaching the symptom of nausea. Furthermore, no significant difference was noted in the total number and severity of symptoms displayed. It appears that the selective peripheral actions of cetirizine and fexofenadine are of no benefit in the prevention or treatment of laboratory-induced motion sickness. The present research raises additional questions regarding the relationship between the sedative action and the antiemetic effectiveness of the H_1 receptor antagonists.

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EXTRACTO

OBJETIVO: Determinar la efectividad de 2 antihistamínicos de segunda generación en la modulación de enfermedad del movimiento inducido por la estimulación del emparejamiento cruzado del vestíbulo Coriolis.

MÉTODOS: Este es un estudio prospectivo, aleatorio, doble ciego, cruzado, y controlado con placebo que incluyó 18 adultos saludables. A los sujetos se les indujo emparejamiento cruzado del vestíbulo Coriolis en el laboratorio utilizando la Prueba de Perfil de la Escalera para la susceptibilidad antes y durante la influencia de cetirizine, fexofenadine, y placebo. La evaluación subjetiva de los síntomas de mareo se basó en la criteria diagnóstica de Graybiel para enfermedad del movimiento aguda, la escala de Golding, y en el Indice de Susceptibilidad de Enfermedad de Coriolis.

RESULTADOS: Las medidas repetidas de las pruebas de ANOVA y de ANOVA no-paramétrica Friedman revelaron que no hubo diferencia significativa en la evaluación de síntomas basado en la criteria de diagnóstica de Graybiel ($p \leq 0.001$), en los síntomas subjetivos de mareo por movimiento ($p \leq 0.001$), ni en el estado de ansiedad ($p \leq 0.001$) antes o después de la exposición al movimiento. Sin embargo, no hubo diferencia significativa entre la susceptibilidad a enfermedad de movimiento antes de terapia y el tratamiento de placebo, cetirizine, y fexofenadine.

CONCLUSIONES: La falla de los antihistamínicos de segunda generación, cetirizine y fexofenadine, en prevenir la enfermedad de movimiento sugiere que la acción terapéutica de esta clase de antihistamínicos contra esta enfermedad puede ser mediada a través de receptores centrales versus periféricos, y que el efecto sedante de otros antihistamínicos, como hidroxizine, podría tener un papel más importante que lo pensado anteriormente en aliviar la enfermedad del movimiento.

Giselle C Rivera-Miranda

RÉSUMÉ

OBJECTIF: Déterminer l'efficacité de 2 anti-histaminiques de deuxième génération à moduler les symptômes du mal des transports induit par l'effet Coriolis suite à une stimulation de l'appareil vestibulaire.

MÉTHODES: Il s'agit d'une étude prospective randomisée à double-insu, en chassé-croisé et contrôlée par placebo chez 18 volontaires sains. Les sujets ont été exposés à l'effet de Coriolis en utilisant le Staircase Profile Test afin de mesurer leur susceptibilité initiale, de même que pendant un traitement avec la cétirizine, la féxofénadine, et un placebo. L'évaluation subjective des symptômes a été mesurée avec l'aide des critères diagnostics de Graybiel pour le mal des transports, de l'échelle de Golding ainsi qu'avec l'index de susceptibilité de l'effet Coriolis.

RÉSULTATS: Les analyses ANOVA et de non-paramétriques de Friedman ont révélé des différences significatives dans l'évaluation des symptômes effectuée avec les critères de Graybiel ($p \leq 0.001$), des symptômes subjectifs du mal des transports ($p \leq 0.001$) et de l'état d'anxiété ($p \leq 0.001$) avant et après l'exposition au mouvement. Cependant, il n'a pas eu de différence significative entre la susceptibilité initiale au mal des transports et le traitement pharmacologique, quel qu'il soit.

CONCLUSIONS: L'inefficacité des anti-histaminiques de deuxième génération, cétirizine et féxofénadine, dans la prévention du mal des transports suggère que leur action thérapeutique pourrait être médiée par la voie centrale plutôt que périphérique. De plus, les effets sédatifs des autres anti-histaminiques, telle que l'hydroxyzine, pourraient jouer un rôle plus important dans le soulagement des symptômes du mal des transports.

Nicolas Paquette-Lamontagne